Paper No. 24

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte BERT VOGELSTEIN,
SUZANNE BAKER,
ERIC R. FEARON, and
JANICE M. NIGRO

Appeal No. 2002-0779
Application No. 08/825,746

HEARD: November 19, 2002

Before WILLIAM F. SMITH, MILLS, and GRIMES, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 4 and 12, all of the claims in the application. Claims 4 and 12 read as follows:

4. A method of supplying wild-type p53 gene function to a cell which has lost said gene function by virtue of a mutation in a p53 gene, comprising:

introducing a portion of a human wild-type p53 gene into a human cell which has lost said gene function such that said portion is expressed in the cell, said portion encoding a part of human wild-

type p53 protein which is required for non-neoplastic growth of said cell, whereby wild-type p53 gene function is supplied to the cell.

12. The method of claim 4 wherein said portion corresponds to a region of the p53 gene in the cell which contains the mutations.

The examiner relies on the following references:

Frömmel et al. (Frömmel), "An estimate on the effect of point mutation and natural selection on the rate of amino acid replacement in proteins," J Mol. Evol., Vol. 21, pp. 233-257 (1985)

Bowie et al. (Bowie), "Deciphering the message in protein sequences: Tolerance to amino acid substitutions," Science, Vol. 247, pp. 1306-1310 (1990)

Hollstein et al. (Hollstein), "p53 Mutations in human cancers," Science, Vol. 253, pp. 49-53 (1991)

Ngo et al. (Ngo), "Computational complexity, protein structure prediction, and the levinthal paradox," Birkhäuser Boston, pp. 490-495 (1994)

Hodgson, "Advances in vector systems for gene therapy," Exp. Opin. Ther. Patents, Vol. 5, No. 5, pp. 459-468 (1995)

Verma et al. (Verma), "Gene therapy – promises, problems and prospects," Nature, Vol. 389, pp. 239-242 (1997)

Anderson, "Human gene therapy," Nature, Vol. 392, pp. 25-30 (1998)

Miller et al. (Miller), "Targeted vectors for gene therapy," J. FASEB, Vol. 9, pp.190-199 (1995)

Claims 4 and 12 stand rejected under 35 U.S.C. § 112, first paragraph, as not enabled by the specification.

We reverse.

Background

The p53 gene encodes a tumor suppressor and the mutation of p53 is associated with cancer. Specification, page 6 ("[M]utational events associated with tumorigenesis occur in the p53 gene."). The specification discloses a

method of "supplying wild-type p53 function to a cell which carries mutant p53 alleles. The wild-type p53 gene or a part of the gene may be introduced into the cell in a vector such that the gene remains extrachromosomal. . . . If a gene portion is introduced and expressed in a cell carrying a mutant p53 allele, the gene portion should encode a part of the p53 protein which is required for non-neoplastic growth of the cell." Page 13. "More preferred is the situation where the wild-type p53 gene or a part of it is introduced into the mutant cell in such a way that it recombines with the endogenous mutant p53 gene present in the cell. Such recombination would require a double recombination event which would result in the correction of the p53 gene mutation. Vectors for introduction of genes both for recombination and for extrachromosomal maintenance are known in the art and any suitable vector may be used." Id.

Discussion

Claim 4 is directed to a method of supplying p53 function to a cell (which has lost p53 function) by introducing into the cell a portion of the human wild-type p53 gene, where the portion of p53 encoded by the gene is "required for non-neoplastic growth" of the cell. Claim 12 adds the limitation that the portion of p53 that is introduced includes the part of p53 that is mutated in the cell to be treated.

The examiner rejected all of the claims on the basis that undue experimentation would have been required to practice the claimed method. However, the examiner has acknowledged that a similar method using a full-length p53 gene is enabled. See the Examiner's Answer, pages 6-7. According to the examiner, a restriction requirement was made in a parent application and

the instant claims were held to be patentably distinct from claims to a method of supplying p53 function to cells using a full-length p53 gene. See the Examiner's Answer, page 6.

> Claims directed to the use of the full length p53 gene were elected for prosecution in the parent application. The parent application 08/035,366, is currently part of an interference before the board, Interference 104,066. . . . [T]he office acknowledges that methods of supplying a wild-type full length p53 gene to cells is [sic] enabled by the instant application. . . . However, the instant case is directed to patentably distinct methods of using portions of the p53 gene.

Specification, page 7 (emphasis in original).

Thus, the issue presented is whether, even though a method of supplying p53 function to a cell using a full-length p53 gene is enabled, it would have required undue experimentation to practice the same method using a part of the p53 gene that encode a functional portion of the p53 protein. The examiner concluded that

> in view of the art recognized unpredictability of determining from sequence data alone whether any "portion" of a gene would be able to fold correctly and exhibit wild type protein activity, the state of the art concerning p53 at the time of filing (i.e. 1992), the lack of guidance provided by the specification concerning the importance of amino acid residues outside of the 132-309 region which affect protein folding and/or p53 activity, the lack of guidance provided by the specification concerning the sequence or characteristics of any "portion" of p53 which is required for non-neoplastic growth, the lack of working examples either in vitro or in vivo which use a wild type p53 gene sequence which is a "portion" of the complete full length wild type sequence, the art recognized unpredictability of

> therapeutic gene delivery to target cell in vivo, and the breadth of the claims, it would have required undue experimentation to practice the invention as claimed.

Examiner's Answer, page 8.

Appellants argue that the references relied on by the examiner are not relevant to the instant claims, because they deal either with the effects of mutations on protein function, while the instant claims are limited to portions of the wild-type p53 sequence. See the Appeal Brief, pages 2-4. Appellants argue that the specification and prior art provide ample guidance to allow those skilled in the art to practice the claimed invention without undue experimentation. Appellants point to the specification's Figure 9, which shows that, of the 393 codons in the p53 gene, the bulk of mutations the inactivate p53 fall between codons 132 and 309. Appellants argue that these data would have led those skilled in the art to expect that at least the portion of p53 between codons 132 and 309 was "required for non-neoplastic growth," as recited in the claims.

Appellants also point to the prior art reference by Steinmeyer providing additional guidance. Appellants characterize Steinmeyer as disclosing that 40 amino acids at the N-terminus and an unspecified portion of the C-terminus of p53 were not required for DNA binding. Since "[b]inding to DNA is the mechanism by which wild-type p53 exerts its biological effect." Appellants assert that "by the priority date of the present application, those of skill in the art knew that portions of p53 were biologically active and would have understood that portions of p53 as recited in claims 4 and 12 need not contain C- or N-terminal amino acids to be functional." Appeal Brief, page 5.

The examiner bears the burden of showing a claimed invention is not enabled. See In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) ("When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application."). We agree with Appellants that the examiner has not carried that burden in this case.

The examiner has provided the starting point for our analysis, by conceding that the specification is adequate to enable claims to a method similar to that of the instant claims, but limited to using a full-length p53 gene. See the Examiner's Answer, page 7. The only additional experimentation required to practice the instant claims, relative to the concededly enabled claims, is determining the parts of the p53 gene that encode a portion of the p53 protein required for non-neoplastic cell growth. The only issue we must decide, therefore, is whether this additional experimentation would be undue.

We agree with Appellants that the specification would have led those skilled in the art to expect that the middle half of the p53 gene (encoding codons 132 to 309) was necessary for function, since mutations in that region resulted in non-functional variants of p53. See the specification, page 6, and Figure 9. We also agree with Appellants that Steinmeyer would have led those skilled in the art to expect that the N-terminal 40 amino acids and part of the C-terminus were not

needed for DNA binding, and therefore were not needed for p53 function. See Steinmeyer, page 504, right-hand column.

Taken together, then, the specification and Steinmeyer indicate that amino acids 132-309 are required for p53 function, and codons 1-40 and a certain number of codons at the N-terminus are not required. Thus, the experimentation required by the instant claims would appear to be limited to determining how many of the amino acids between positions 41 and 131, and how many of the codons between positions 310 and the C-terminal 393, could be deleted without adversely affecting the function of p53.

We agree with Appellants that this experimentation would not appear to be undue. At most, the skilled artisan would be required to make and test a series of deletion mutants of p53. This experimentation might be tedious, but it would not seem to be undue. See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) ("[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.").

The examiner's evidentiary references do not appear to be on point. Bowie, Ngo, and Frommel all address the unpredictable effects that point mutations can have on the function of an encoded protein. Here, however, the

claims are limited to portions of the wild-type human p53 gene. Thus, the unpredictability evidenced by the references is not relevant to the claimed method. The examiner also cites several references as evidence that gene therapy was considered highly unpredictable as of the application's effective filing date. See the Examiner's Answer, pages 12-13. However, the examiner has conceded that the instant claims would be enabled if limited to the full-length p53 gene. The examiner has not explained why the asserted unpredictability of gene therapy raises an enablement problem for the instant claims but not for claims to the same method, carried out using a full-length p53 gene. In view of the Office's conclusion that claims limited to using a full-length p53 gene to supply p53 function are enabled by the instant specification, we do not find the examiner's concerns regarding gene therapy to be well-founded.

Summary

The examiner has not adequately shown that it would have required undue experimentation to determine which parts of the p53 gene encode portions of p53 required for non-neoplastic cell growth. Therefore, and since the examiner has conceded that the presently claimed method would be enabled if limited to the full-length p53 gene, we agree with Appellants that a prima facie

case of nonenablement has not been made. The rejection under 35 U.S.C. § 112, first paragraph, is reversed.

REVERSED

WILLIAM F. SMITH Administrative Patent Judge	)
DEMETRA J. MILLS Administrative Patent Judge	) BOARD OF PATENT) APPEALS AND) INTERFERENCES
ERIC GRIMES Administrative Patent Judge	)

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